Case Reports

Nitrofurantoin-Induced Cholestatic Hepatitis From Cow's Milk in a Teenaged Boy

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ACUTE HEPATOTOXIC reactions to nitrofurantoin, a frequently prescribed antibiotic, are rare.[1,2] We report a case of nitrofurantoin-induced cholestatic hepatitis in which the offending agent had been unknowingly ingested in cow's milk.

Report of a Case

The patient, a 16-year-old male high school student was admitted to Longmont (Colorado) United Hospital in late May of 1981 because he had had epigastric and right upper quadrant pain for three days. The pain was aching and cramping and associated with nausea and vomiting. One day before admission, an erythematous rash involving the palms and soles developed. On the day of admission, he noticed jaundice and had the onset of fever and chills.

The patient lived on a small farm in northern Colorado. He said he had not had contact with rodents, insect bites nor had he drunk untreated water. He consumed no alcohol and did not take prescription, over-the-counter or illicit drugs. No household contacts or friends were jaundiced, and he had not left the local area within the past year. He had no medical history of serious illness, hospital admissions or transfusions.

On physical examination, he appeared thin and jaundiced. His blood pressure was 110/80 mm of mercury, pulse rate was 96 and oral temperature 38.3°C (100.9°F). The sclerae were icteric; there was no conjunctival injection. The skin was icteric and there was a maculopapular eruption involving the skin of the soles and palms. The oral mucosa appeared normal. Examination of the heart and lungs elicited no abnormalities. The abdomen was flat and bowel sounds were normal. The liver margin was palpable at the right costal margin on deep inspiration; its edge was rounded, firm and tender; the spleen was not palpable. Urogenital, neuromuscular and joint examinations showed no abnormalities.

Laboratory studies disclosed the following values (normal range is given in parentheses): hematocrit, 42%; leukocyte count, 15,900 per μl, with 68% segmented and 2% banded neutrophils, 23% lymphocytes, 2% monocytes and 5% eosinophils. Serum alkaline phosphatase, 33.1 IU per liter (4.5 to 11); serum aspartate amino transferase, 68 IU per liter (22 to 47); serum bilirubin, 15.4 mg per dl, direct reacting, 8.2 mg per dl. Prothrombin time was normal; analysis of urine was positive for acetone and bilirubin but negative for albumin, blood and leukocytes. The following tests gave negative results: rapid plasma reagin, Monospot and heterophile agglutination, hepatitis B surface antigen, core and surface antibody, hepatitis A antibody, febrile agglutinins including Weil-Felix, antinuclear antibodies and *Leptospira* agglutinins. Cultures of three blood specimens taken at the time of admission grew no organisms. Abdominal ultrasound studies showed a normal gallbladder free of stones; neither the extrahepatic nor the intrahepatic ducts were dilated.

For five days after admission, the patient remained intermittently febrile with oral temperatures as high as 39.2°C (102.6°F). The skin eruption became desquamative. The leukocyte count rose to 25,400 per μl with 6% eosinophils and the serum alkaline phosphatase level reached 66 IU per liter.

A percutaneous liver biopsy was done seven days after admission. Histologic examination showed the lobular architecture of the liver to be intact. There was moderate centrilobular cholestasis with only occasional canalicular plugs; ballooning and feathery degeneration were absent. A few Councilman-like bodies were noted, some being surrounded by small aggregates of lymphocytes and histiocytes. The sinusoids contained occasional lymphocytes and eosinophils. Kupffer's cells were focally distended with periodic acid-Schiff (PAS)-positive, diastase-resistant material. Hepatocellular mitoses and binucleate cells were numerous (Figure 1). Most portal tracts were expanded by edema and a dense, predominantly neutrophilic and eosinophilic infiltrate; the neutrophils invaded many bile ducts and often were associated with epithelial necrosis and plugging of the duct lumen with eosinophilic debris (Figure 2). The limiting plates were intact. There was no fibrosis and no granulomata were found.

Because the findings of this liver biopsy were suggestive of toxic rather than viral hepatitis, the patient was requestioned about any drug ingestion. This was denied again; however, he had learned that he had consumed milk from cows that had been treated paren-

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terally with nitrofurantoin. The cows had received nitrofurantoin parenterally during the week preceding the patient's illness and had no overt adverse reactions. Over the next few days, the patient became afebrile; the leukocyte count and serum bilirubin and alkaline phosphatase values returned to normal. The patient has remained asymptomatic for over a year.

Discussion

The incidence of adverse reactions to nitrofurantoin has been as high as 9.2%,[1] but hepatotoxic reactions seem to be rather uncommon. Thus, in a prospective study of 757 patients treated with the drug, no hepatic injury was seen.[1] In 921 adverse reactions reported voluntarily to the Swedish Adverse Drug Reaction Council, only 5% involved the liver.[2]

Acute hepatotoxic reaction of both the cholestatic[3-9] and hepatocellular type[10,11] have been described. Nitrofurantoin has also been implicated in the development of chronic liver disease[12,13] and the evidence for this has been reviewed editorially.[14] Recently, a case each of granulomatous hepatitis[15] and of focal nodular hyperplasia[16] have been ascribed to nitrofurantoin.

The present case is remarkable for three features: its occurrence in a teenaged boy, transmission of the offending agent by cow's milk and the presence of pronounced cholangiolitic lesions on examination of the liver biopsy specimen.

The age of patients who had acute liver injury due to nitrofurantoin ranged from 31 to 84 years, 80% of the patients being women.[3-11] Thus, our patient is by far the youngest and only the third male patient to have nitrofurantoin-induced hepatotoxic reaction. This presumably reflects the prescription pattern of the drug rather than any age- or sex-related difference in susceptibility.[14]

Transmission of drug toxicity by milk is a well-recognized phenomenon.[16] Nitrofurantoin achieves a milk-to-plasma ratio of 0.3 in humans.[17] By contrast, nitrofurantoin was not detectable by a bioassay of cow's milk after intrauterine administration.[18] This could be due to the insensitivity of the assay used or to inadequate bioavailability after intrauterine administration.[18]

Neither the physiochemical properties of the drug nor species differences in milk secretion suggest that nitrofurantoin is excreted into human but not cow's milk.[16] The clinical presentation of our patient with fever, rash and eosinophilia is typical of the cholestatic form of nitrofurantoin toxicity. These signs were present in 60%, 30% and 70%, respectively, of the 18 patients reviewed by Zimmerman[19] and in four, six and five, respectively, of the six patients with cholestatic hepatitis.[3,5-9] Final proof for the involvement of a particular drug in hepatotoxic reactions can often be obtained only by a positive rechallenge with the offending agent. A positive response to reexposure has been described in several instances.[3,5,9,11] However, in view of the severity of the presentation in our case and of reported fatalities,[2,7] it was felt unethical to rechallenge a young man who probably will never need to use the drug again.

The histologic picture in our case is compatible with nitrofurantoin-induced cholestatic injury. Thus, predominantly centrilobular cholestasis without feathery degeneration has been described.[3,5] Even in predominantly cholestatic liver disease, focal inflammation and mild hepatocellular damage have been seen.[3,9] An abundance of binucleate cells and increased mitotic activity (Figure 1) have also been commented on.[3] A few Councilman-like bodies are usually associated with the hepatocellular form.[11] The PAS-positive, diastase-resistant material in Kupffer's cells encountered in our case has previously been described only in a case with hepatocellular injury.[11] The pronounced eosinophilic portal and sinusoidal infiltrate, typical of drug-induced hepatic injury, has been reported in several cases.[3,9,11] An unusual feature in our case was the marked involvement of the portal bile ducts with edema, neutrophilic invasion of the ductular epithelium and, finally,

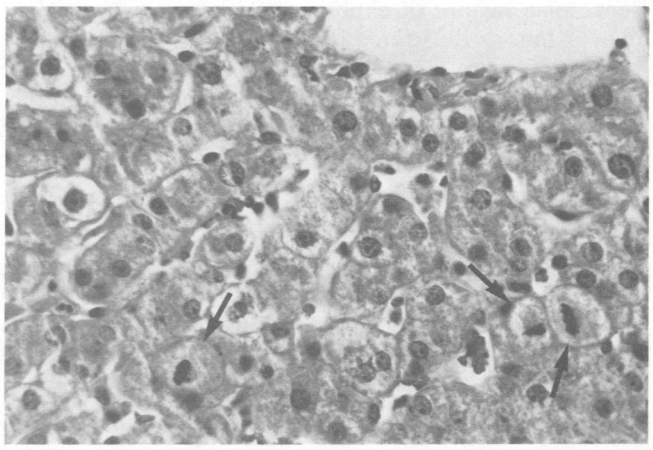

Figure 1.—A high-power photomicrograph shows three liver cell mitoses **(arrows),** indicating regeneration near the central vein. There is no hepatocellular necrosis. (Hematoxylin-eosin stain, reduced from magnification ×410.)

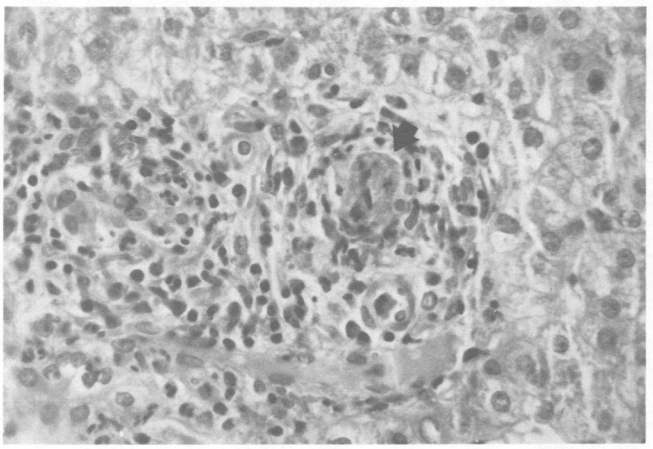

Figure 2.—A portal tract infiltrated by neutrophils and eosinophils. An interlobular bile duct is plugged by necrotic epithelial cells **(arrow).** (Hematoxylin-eosin stain, reduced from magnification ×410.)

sloughing of necrotic cells into the ductular lumen (Figure 2). This presents a necrotizing cholangiolitis of a severity not previously recognized. Only one previous case showed some evidence of cholangiolitis but to a much lesser extent.[5]

The mechanism of action of nitrofurantoin in inducing acute or chronic liver cell injury is still debated. The presence of a variety of immunologic epiphenomena, an association with HLA-B8 in chronic hepatitis[12] and the pronounced eosinophilic infiltrate in acute hepatotoxic reaction[3] led to the postulate of an immune, possibly genetically mediated injury. The rarity of hepatocellular injury has also been taken as evidence of a hypersensitivity reaction.[19] The evidence for this has been critically reviewed and certainly is not conclusive.[14] Formation of reactive intermediates such as superoxide radicals has been found in several systems.[20,21] Furane derivatives have been found to be hepatotoxic in mice.[22] The relevance of these recent findings to toxic effects in humans is unknown.

Identifying the cause of a toxic reaction in the absence of a history of exposure can be a frustrating endeavor but, as illustrated by this case, is not necessarily a hopeless one. Cow's milk most likely served as the unsuspected vehicle for transmission of nitrofurantoin, producing a severe cholestatic hepatitis in a host of uncharacteristic age and sex for this particular drug reaction.

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Pancreatic Involvement in Hippel-Lindau Disease

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HIPPEL-LINDAU DISEASE is an uncommon autosomal dominant disease characterized by hemangioblastomas of the retina and the central nervous system. A variety of other cystic and neoplastic lesions can be found widely dispersed throughout the body, including cysts of the abdomen and neoplasms of the kidney, adrenals and sympathetic chains. Although many clinicians are aware that retinal and cerebellar lesions occur as part of the disease, the potential for multiorgan involvement is not generally appreciated. Visceral involvement, though often clinically silent, may be present.

We describe a case of Hippel-Lindau disease in which there was extensive pancreatic involvement in addition to lesions of the central nervous system.

Report of a Case

A 21-year-old Vietnamese man known to have retinal angiomatosis came to the University of California Irvine Medical Center because he had had headache, nausea, vomiting and dizziness for three weeks. He had had no weakness or sensory changes. On examination his left eye showed papilledema and increased vascularity, consistent with angioma. The patient had been observed since 1980 and had received periodic laser coagulation for preservation of his vision. He had previously undergone enucleation of the right eye because of an extensive angioma.

A computed tomographic (CT) scan of the head showed acute hydrocephalus and a large right cerebellar cyst. An angiogram showed two right-sided cerebellar hemangiomas. We excised the hemangiomas by a right suboccipital craniectomy. During the operation the surgeon found a 3-cm cyst in the posterior fossa anterior to the cerebellar hemangioma. The patient recovered from the neurosurgical procedure and his preoperative symptoms resolved.

To discover whether there was visceral involvement, an intravenous pyelogram and a CT scan of the abdomen were done. The pyelogram showed no abnormalities. A very large retroperitoneal mass could be seen on the CT scan (Figure 1). To assure that a heman-

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